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RECEIVED 05 October 2024

ACCEPTED 11 November 2024

PUBLISHED 17 December 2024

CITATION

Chaudhary P (2024) Oxidative coupling of *N*-nitrosoanilines with substituted allyl alcohols under rhodium (III) catalysis.
Front. Chem. 12:1506493.
doi: 10.3389/fchem.2024.1506493

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Oxidative coupling of *N*-nitrosoanilines with substituted allyl alcohols under rhodium (III) catalysis

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Rhodium(III) catalysis has been used for C-H activation of *N*-nitrosoanilines with substituted allyl alcohols. This method provides an efficient synthesis of the functional *N*-nitroso *ortho* β -aryl aldehydes and ketones with low catalyst loading, high functional group tolerance, and superior reactivity of allyl alcohols toward *N*-nitrosoanilines. We demonstrated that reaction also proceeds through the one-pot synthesis of *N*-nitrosoaniline, followed by subsequent, C-H activation. The protocol was also feasible with acrylaldehyde and methyl vinyl ketone which furnished the same oxidative *N*-nitroso coupling product.

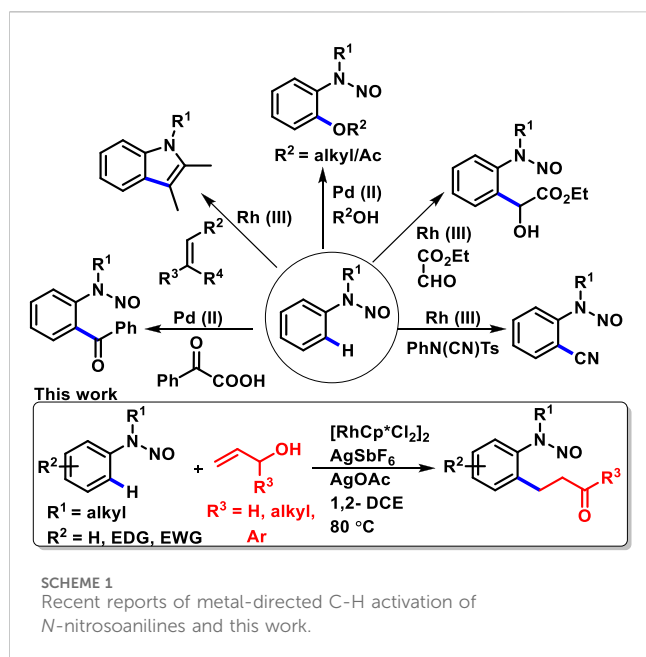
KEYWORDS

N-nitrosamines, oxidative coupling, allyl alcohols, rhodium (III) catalysis, C-H activation and functionalization

Introduction

Transition metal-catalyzed reactions have a great impact on the synthesis of natural products and in medicinal chemistry (Crawley and Trost, 2011; Du Bois, 2011; Hayler et al., 2019; Brandsma et al., 1999). They have been proven to be the promising and key-driven strategy for the C-H activation of functionalized arenes. In this context, traditional palladium-catalyzed C-H olefination (the oxidative Heck reaction or Fujiwara–Moritani reaction) has been known for generating a new C-C bond (Oestreich, 2009; Moritani and Fujiwara, 1967; Fujiwara et al., 1969). Later, in 2000, Matsumoto disclosed the rhodium-catalyzed oxidative Heck reaction (Matsumoto and Yoshida, 2000; Matsumoto et al., 2002). Furthermore, various research groups have significantly contributed toward rhodium-catalyzed C-H functionalization (Colby et al., 2009; Tian and Loh, 2015; Huang et al., 2013; Li B. et al., 2015; Deng et al., 2016; Kim et al., 2017; Font et al., 2018; Wu et al., 2019; Shi et al., 2020). In this respect, transitory directing groups have reached a remarkable milestone. Indeed, among the various nitrogen-based directing groups (amide, amine, imine, pyridine, pyrimidine, and pyrazole), we focused on *N*-nitrosoanilines with all the key features, which can be transformed to various prevalent structural motifs with significant synthetic and biological importance.

N-nitrosamines are chemical compounds that are extensively found in naturally active molecules and also in a range of food and cosmetic products (Loepky and Outram, 1982; Loepky and Michejda, 1994; Wang et al., 2005). The chemistry of *N*-nitrosamines has gained interest in organic and medicinal chemists. In this respect, *N*-nitrosoanilines are found to be a very attractive directing group as they can be easily removed and installed (Chaudhary et al., 2016a; Chaudhary et al., 2018). *N*-nitrosamines belong to a versatile class of compounds as they serve as important building blocks. They have become valuable intermediates, which are generally used as an anchor for further transformation, such as reduction to hydrazines

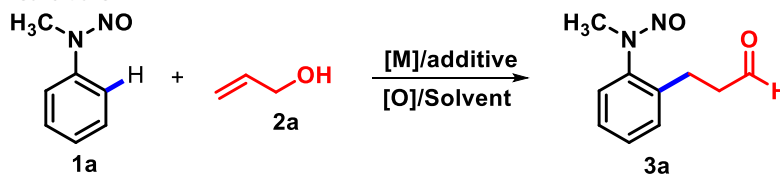


(Hartman and Roll, 1933; Chaudhary et al., 2016b) and amines (Chaudhary et al., 2018), synthesis of mesoionic-heterocyclic compound sydones (Stewart, 1964; Browne and Harrity, 2010) and

aryl C-nitroso compounds through Fischer–Hepp rearrangement (Williams, 1975; Cikotiene et al., 2013), and, also, derivatization at the α -carbon of *N*-nitrosamines (Seebach and Enders, 1975). In addition to these, recently, *N*-nitrosoanilines have emerged as a traceless directing group since the nitroso functionality possesses the lone pair which can coordinate with the transition metal for the activation of the inert C-H bond (Lee et al., 2002). Several research groups have developed metal-catalyzed *ortho*-functionalization of *N*-nitrosoanilines, for example, alkenylation, acylation, alkoxylation, acyloxylation, and cyanation (Scheme 1) (Liu B. et al., 2013; Wu et al., 2016; Gao and Sun, 2014; Li D.-D. et al., 2015; Dong et al., 2015; Huang et al., 2016; Xiong et al., 2023). Despite this recent progress in the C-H functionalization of *N*-nitrosoanilines, to the best of our knowledge, the oxidative alkylation of *N*-nitrosoanilines with allyl alcohols has not been reported. Allyl alcohols serve as immensely important building blocks in organic synthesis and have been explored as a reaction partner for C-H functionalization (Wang et al., 2018; Chen et al., 2012; Wang et al., 2019; Ouyang et al., 2022). Herein, we report rhodium-catalyzed regioselective *ortho* C-H oxidative alkylation of *N*-nitrosoanilines with various substituted allyl alcohols to provide valuable functional *N*-nitroso *ortho* β -aryl aldehydes and ketones (Scheme 1).

Our investigation to optimize reaction conditions began with the reaction of *N*-methyl *N*-nitrosoaniline (**1a**) and allyl alcohol (**2a**) under different catalysts, additives, and solvents (Table 1). Initially, we studied that the reaction of **1a** with **2a** in the presence of

TABLE 1 Optimization of reaction conditions^a.



Entry	Catalyst (mol %)	Additive (mol %)	Oxidant (mol%)	Solvent	Temp. (°C)	Yield (%) ^[b]
1	[RhCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (10)	–	1,2-DCE	80	00
2	[RhCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (10)	Cu(OAc) ₂ (100)	1,2-DCE	80	60
3	[RhCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (10)	Ag ₂ CO ₃ (100)	1,2-DCE	80	46
4	[RhCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (10)	NaOAc (100)	1,2-DCE	80	31
5	[RhCp*Cl ₂] ₂ (5.0)	AgSbF ₆ (20)	AgOAc (100)	1,2-DCE	80	67
6	[RhCp*Cl ₂] ₂ (5.0)	AgSbF ₆ (10)	AgOAc (200)	1,2-DCE	80	61
7	[RhCp*Cl ₂] ₂ (5.0)	AgSbF ₆ (10)	AgOAc (50)	1,2-DCE	80	63
8	[RhCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (10)	AgOAc (100)	1,2-DCE	80	82
9	[RhCp*Cl ₂] ₂ (1.0)	AgSbF ₆ (10)	AgOAc (100)	1,2-DCE	80	75
10	[RhCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (20)	AgOAc (100)	1,2-DCE	80	79
11	[RhCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (5)	AgOAc (100)	1,2-DCE	80	68
12	[RhCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (10)	AgOAc (100)	CH ₃ CN	80	15
13	[RhCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (10)	AgOAc (100)	1,4-Dioxane	100	32
14	[RhCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (10)	AgOAc (100)	THF	65	21
15	[RhCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (10)	AgOAc (100)	MeOH	80	11
16	–	AgSbF ₆ (10)	AgOAc (100)	1,2-DCE	80	00
17	[RhCp*Cl ₂] ₂ (2.5)	–	AgOAc (100)	1,2-DCE	80	33
18	[Ru(p-cymene)Cl ₂] ₂ (2.5)	AgSbF ₆ (10)	AgOAc (100)	1,2-DCE	80	<5
19	[IrCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (10)	AgOAc (100)	1,2-DCE	80	13

^aReaction conditions: **1a** (0.5 mmol) and **2a** (0.6 mmol) in the solvent (3 mL) under a N₂ atmosphere.

^bIsolated yield after column chromatography.

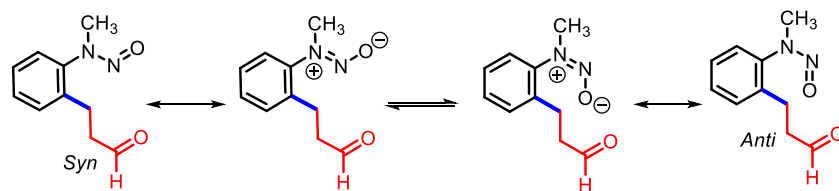
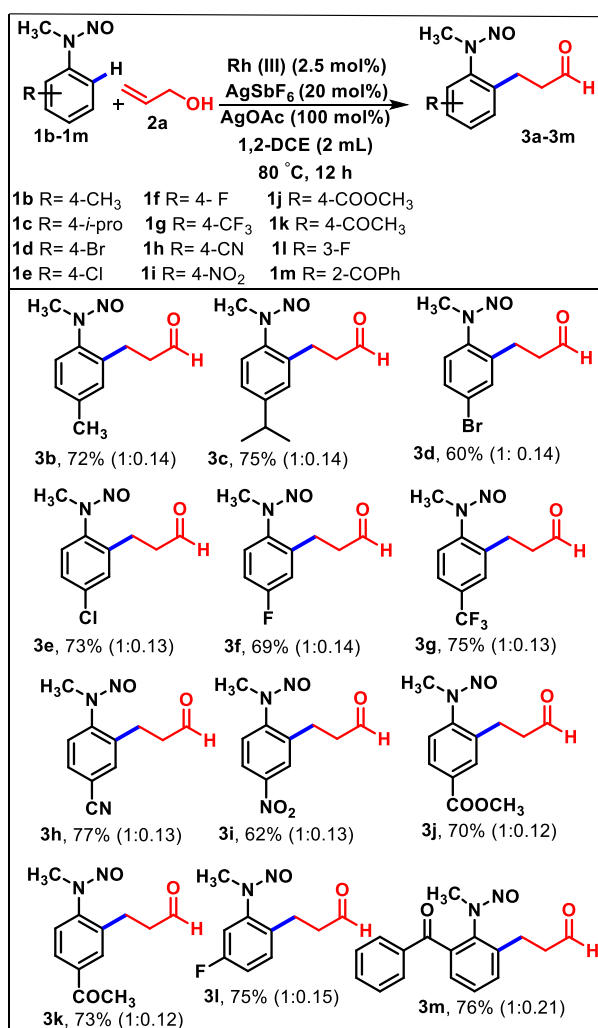


FIGURE 1
Syn and anti orientation of 3a (Liu B. et al., 2013).

TABLE 2 Substrate scope of various *N*-nitroso *N*-alkyl nitrosoanilines 1b–1m and allyl alcohol 2a^{a,b,c}.



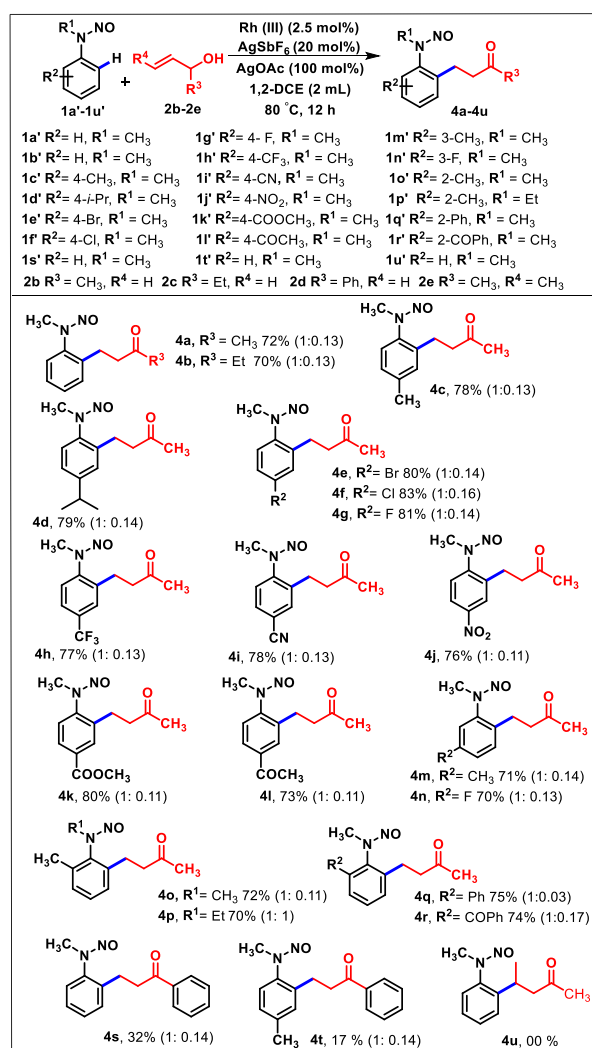
^aReactions were performed with **1** (0.5 mmol, 1.0 equiv.) and **2** (0.6 mmol, 1.2 equiv.) in DCE (3 mL) at 90°C for 12 h under a N₂ atmosphere.

^bIsolated yield.

^cRatio of *syn* to *anti* isomers, determined using the ¹H NMR spectrum.

[RhCp*Cl₂]₂ (5 mol%) and AgSbF₆ (10 mol%) in 1,2-dichloroethane (DCE) at 80°C for 12 h did not provide any product. (Table 1, entry 1). Therefore, the role of additives was examined for any improvement in the reaction. The employment of 100 mol% of Cu(OAc)₂, Ag₂CO₃, NaOAc, and AgOAc in dichloroethane at 80°C for 12 h afforded **3a** with 60, 46, 31% and 67% yields, respectively

TABLE 3 Substrate scope of various *N*-nitroso *N*-alkyl nitrosoanilines 1a'-1u' and substituted allyl alcohol 2b-2e^{a,b,c}.

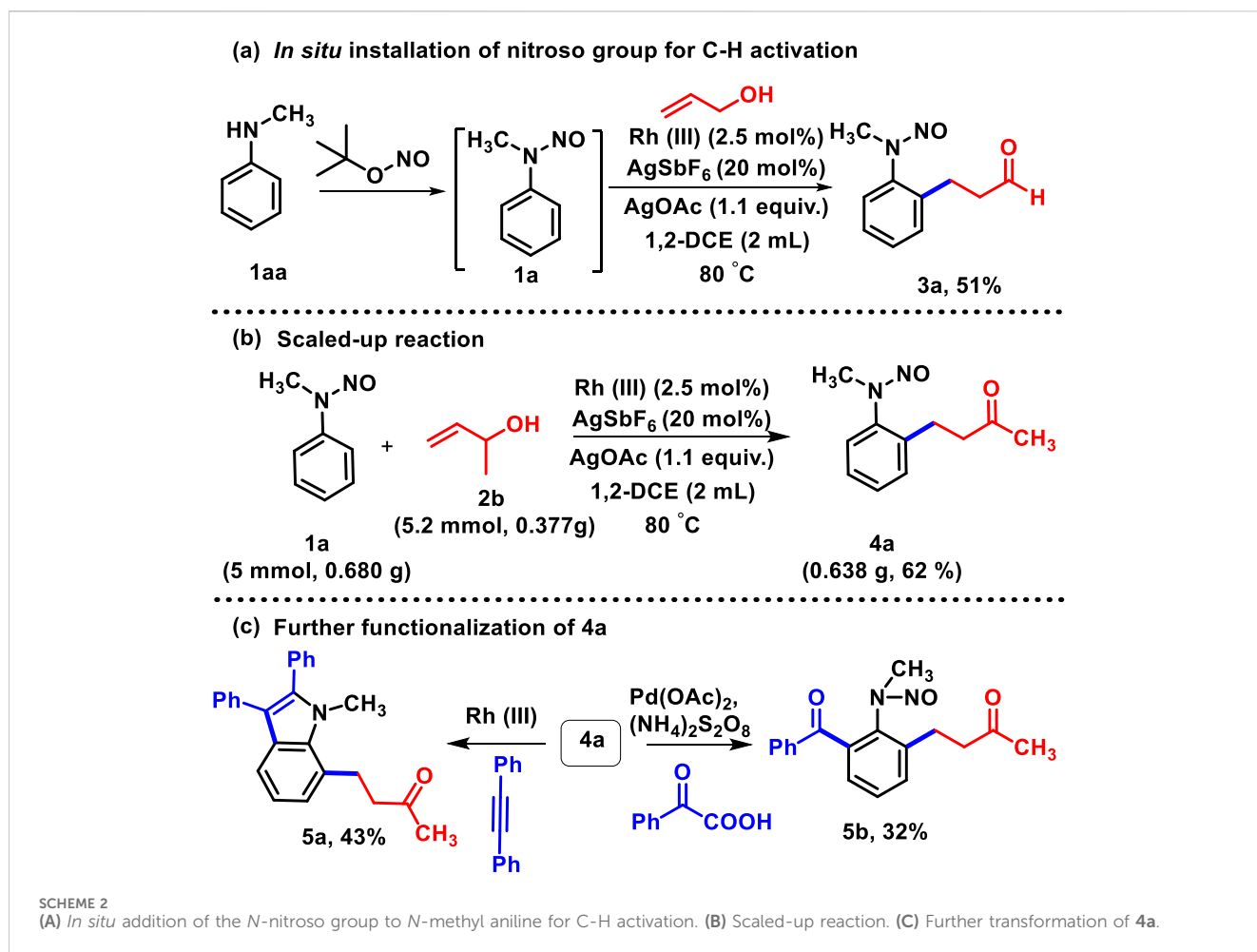


^aReactions were performed with **1** (0.5 mmol, 1.0 equiv.) and **2** (0.6 mmol, 1.2 equiv.) in DCE (3 mL) at 90°C for 12 h under a N₂ atmosphere.

^bIsolated yield.

^cRatio of *syn* to *anti* isomers, determined using the ¹H NMR spectrum.

(Table 1, entries 2–5). An increase or decrease in the amount of AgOAc from 200 mol% to 50 mol% did not affect the yield of the desired product **3a** (Table 1, entries 6 and 7). However, decline in the loading of the [RhCp*Cl₂]₂ catalyst to 2.5 mol% along with AgSbF₆ (10 mol%) and 100 mol% of AgOAc in DCE at 80°C for 12 h



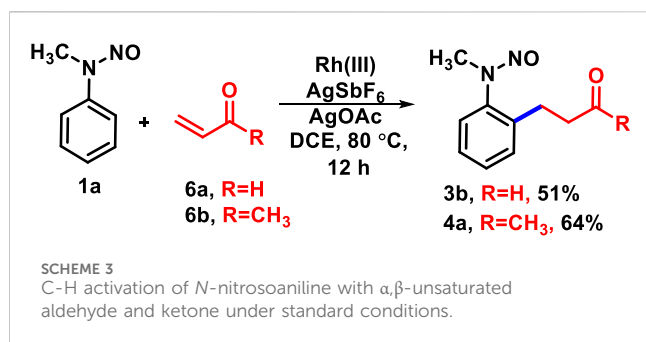
provided a high yield of **3a** (82%) (Table 1, entry 8). The product **3a** was obtained as *syn*- and *anti*-isomers in 1: 0.13 ratio. Furthermore, the decrease in the amount of the $[\text{RhCp}^*\text{Cl}_2]_2$ catalyst to 1 mol% was experimented for 12 h, which lowered the yield of **3a** to 75% (Table 1, entry 9). However, any increase or decrease in the amount of AgSbF_6 from 20 mol% to 5 mol% did not enhance the yield (Table 1, entries 10 and 11). Later, the effect of the solvents was explored. In non-polar and polar solvents such as CH_3CN , 1,4-dioxane, THF, and MeOH, **3a** was obtained in 15, 32, 21%, and 11% yields, respectively (Table 1, entries 12–15).

In the absence of the $[\text{RhCp}^*\text{Cl}_2]_2$ catalyst, no product was detected with AgSbF_6 and AgOAc in 1,2-DCE (Table 1, entry 16), whereas the absence of AgSbF_6 leads to a lower yield of **3a** (33%) (Table 1, entry 17) in the presence of 2.5% $[\text{RhCp}^*\text{Cl}_2]_2$. Furthermore, other catalysts such as $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ and $[\text{IrCp}^*\text{Cl}_2]_2$ were found to be less efficient compared to $[\text{RhCp}^*\text{Cl}_2]_2$ for the transformation (Table 1, entries 18 and 19). The ^1H NMR spectrum of **3a** showed distinctive signals for adjacent methylene ($-\text{CH}_2-\text{CH}_2-$) protons to aldehyde (δ 2.76 and δ 2.86 ppm as a triplet, $J = 7.4$ Hz), and the aldehyde singlet proton was observed at δ 9.75 ppm. The ^{13}C NMR spectrum of **3a** showed a representative signal for the adjacent methylene carbon to aldehyde, which was observed at 44.7 ppm, and the next methylene carbon to it was observed at 23.8 ppm; the carbonyl group of the aldehyde was observed at 200.5 ppm. **3a** was obtained as a mixture of *syn* and *anti*

at a ratio of approximately 1: 0.13 (determined using the ^1H NMR spectrum) with 82% yield (Figure 1).

Having established the optimized condition, the reaction of substituted *N*-nitroso *N*-alkyl anilines was investigated with allyl alcohol. Treatment of **2a** with several substituted *N*-nitroso *N*-alkyl anilines, namely, **1b–1m**, bearing electron-donating and electron-deficient groups, was observed (Table 2). The *p*-substituted electron-donating *N*-nitroso *N*-methyl anilines (methyl and isopropyl) were converted to the corresponding products **3b** and **3c** with good yields (72% and 75%, respectively). Similarly, the substrates bearing halide groups such as Br, Cl, and F at the *para* position under optimized conditions provided the desired products **3d–3f** with good yields (60%–73%). It is noteworthy that other *p*-substituted functionalities that have strong electron-withdrawing tendencies, such as trifluoromethyl, cyano, nitro, ester, and acetyl groups, provided the expected products **3g–3k** with 62%–77% yields in 12 h.

The oxidative alkylation of *m*-fluoro *N*-methyl *N*-nitrosoaniline also yielded the expected product **3l** away from the sterically hindered position with 75% yield. Later, the attempted reaction of sterically hindered **1m** with **2a** regioselectively afforded the *ortho*-substituted (2-benzoyl-6-(3-oxopropyl) phenyl)-*N*-methyl *N*-nitrosoaniline (**3m**) smoothly with 76% yield. Overall, the simple allyl alcohol underwent C-C bond formation effectively with a range of *N*-nitrosoanilines of varying electronic and steric factors.

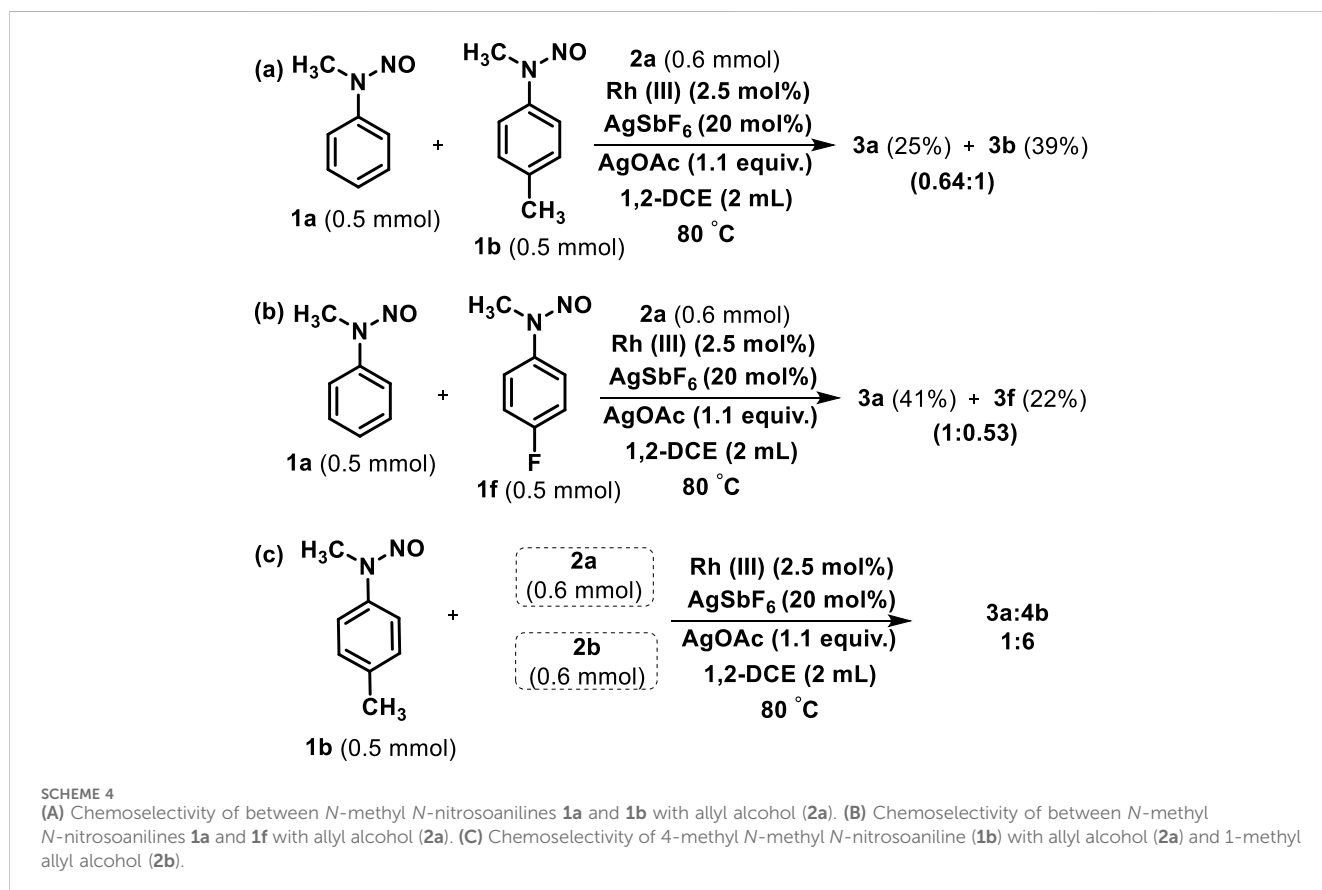


On account of these results, under the assistance of *N*-nitroso as a directing group, we attempted to explore the reactivity of substituted allyl alcohol **2b–2d** toward different *N*-alkyl *N*-nitrosoanilines (Table 3). The unsubstituted nitrosoaniline reacted with 1-methyl and 1-ethyl, which yielded the corresponding products **4a** and **4b** in 72% and 70%, respectively. Similarly, the oxidative alkylation of the *p*-substituted electron-donating substrate (-Me and -^{*i*}Pr) provided the corresponding β -aryl ketones **4c** and **4d** in good yields (78% and 79%). In addition, aryl halides such as bromide, chloride, and fluoride at the *p*-position were found to be stable during the reaction conditions and produced the products **4e**, **4f**, and **4g** with 80%, 83%, and 81% yield, respectively. Furthermore, the sensitive functionalities, such as 4-CF₃, 4-CN, 4-COOCH₃, and 4-COCH₃, on the benzene ring of *N*-nitrosoanilines were allowed to react with **2b**, as a result of which **4h–4l** were successfully isolated with 73%–80% yield. Moreover, the

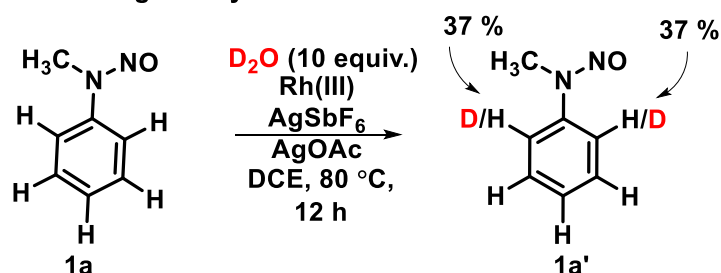
reaction of **2b** with *m*-substituents such as methyl and fluoro nitrosoanilines afforded the corresponding products **4m** and **4n** with 71% and 70% yield, respectively. C-H activation occurred toward a less sterically hindered position of nitrosoaniline. The variation in *N*-alkyl substitution of 2-methyl *N*-nitrosoaniline from methyl **1o'** to ethyl **1p'** was found to have well-participated under the standard reaction conditions, and products **4o** and **4p** were obtained in good yields (70%–72%). The other *N*-methyl nitrosoanilines containing *o*-substituents such as -Ph and -COPh provided the products **4q** and **4r** in 75% and 74% yields, respectively. This indicates that the protocol has the least influence of steric encumbrance of *ortho*-substituents. Intriguingly, we investigated that the reaction of **1a'** with 1-phenyl allyl alcohol (**2d**) yielded the products **4s** and **4t** in 32% and 17% yields, respectively. Moreover, the combination of **1a'** with pent-3-en-2-ol (**2e**) was also inspected, but no product was observed. This may be due to the steric influence of the methyl group of **2e**, which hindered the oxidative coupling to *N*-methyl *N*-nitrosoaniline (**1a'**).

Regarding C_{sp2}-C_{sp2} bond formation, we attempted one-pot synthesis (Hayashi, 2016), where the addition of the nitroso group (Chaudhary et al., 2018) to *N*-methyl aniline (**1aa**) leads to the corresponding nitrosoaniline, and fortunately, we obtained the oxidative coupled product (**3a**) under the standard reaction conditions with 51% yield (Scheme 2A).

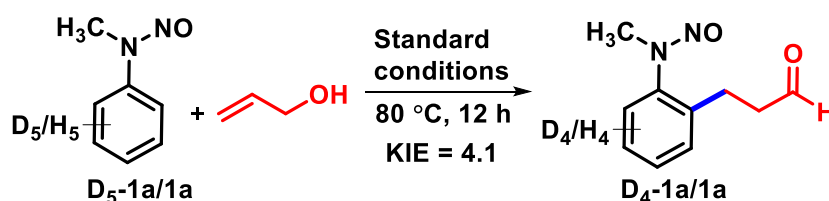
Henceforth, the protocol exemplifies that implementation of a nitroso unit and subsequent oxidative C-H activation with allyl alcohol reduces time and labor, which, obviously, displays its advantages. To show the synthetic utility of the protocol, the gram-scale synthesis of **4a** had been performed (Scheme 2B) and



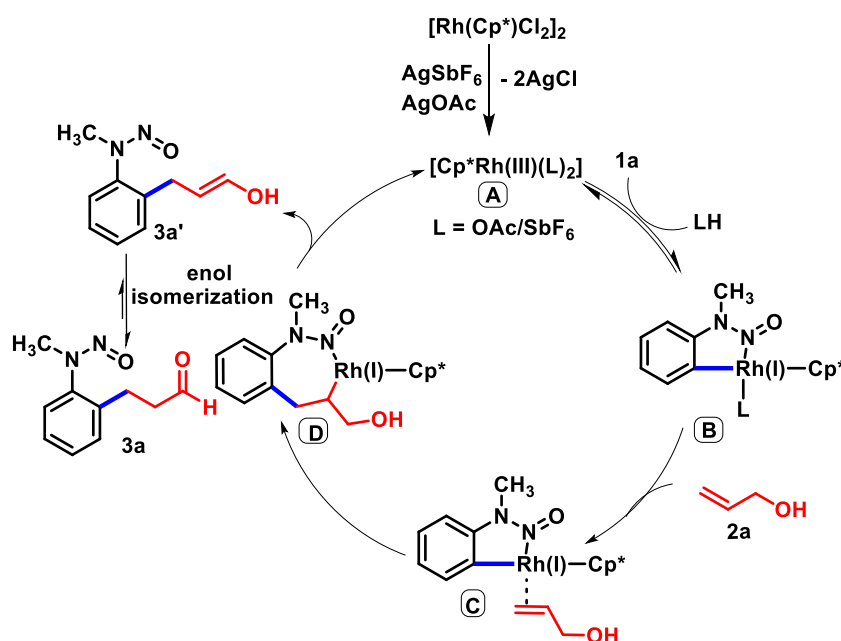
(a) H/D exchange study



(b) Kinetic Isotopic Effect (KIE) study



SCHEME 5
Preliminary mechanistic studies. (A) H/D Exchange Study. (B) Kinetic Isotopic Effect (KIE) Study.



SCHEME 6
Proposed mechanism.

the product was obtained with 62% yield, which was utilized for different transformation processes (Scheme 2C). Versatile *N*-nitroso directing allowed further catalyzation of C-H activation of 4b at the other *ortho*-position with rhodium (Liu B. Q. et al., 2013) and palladium (Wu et al., 2016). The activation with diphenyl acetylene and phenyl glyoxylic acid yielded the desired products 5a and 5b with 43% and 32% yields, respectively. In the course of our study, we performed the reaction of *N*-nitrosoaniline under the same reaction

conditions with acrylaldehyde and methyl vinyl ketone. To the best of our knowledge, only β -hydride-eliminated products were obtained such as 3b and 4a; no olefinated or protonolysis product was observed (Scheme 3) (Sun et al., 2010; Peng et al., 2012).

The chemoselectivity of two different *N*-methyl *N*-nitrosoanilines toward allyl alcohol (2a) was examined under the standard reaction conditions (Scheme 4A). First, the reaction of the unsubstituted (1a) and 4-methyl *N*-methyl *N*-nitrosoaniline (1b)

subjected to react with allyl alcohol (**2a**) for 12 h led to the respective products **3a** and **3b** with 25% and 39% yields, respectively (Scheme 4; Scheme 4A). Similarly, treatment of unsubstituted (**1a**) and 4-fluoro *N*-methyl *N*-nitrosoaniline (**1f**) with **2a** afforded the products **3a** and **3f** with 41% and 22% yields, respectively (Scheme 4B). The results indicated that the *N*-nitrosoaniline bearing the electron-donating group is more chemoselective than the unsubstituted and electron-withdrawing bearing substrate. Even the chemoselectivity of 4-methyl *N*-methyl *N*-nitrosoaniline (**1b**) toward allyl alcohol (**2a**) and 1-methyl allyl alcohol (**2b**) was also investigated, which demonstrated the formation of **3a:4b** in the ratio of 1:6 at the same refractive index (R_f) (Scheme 4C). These intermolecular competitive reactions indicate the simultaneous formation of rhodium carbon and the cleavage of the C-H bond probably by a concerted metalation mechanism (CMD) (Lapointe and Fagnou, 2010).

To gain mechanistic insights, we conducted deuterium labeling experiments, as shown in Scheme 5. The H/D exchange experiment was carried out with 2.5 mol% Rh(III), AgSbF₆ (10 mol%), and AgOAc (1 equiv.) to yield **1a** (Scheme 5A). The incorporation of 37% deuterium was observed at *ortho* positions of **1a**, which revealed that the C-H activation step is reversible. The parallel kinetic isotopic effect (KIE) was evaluated through an experiment with **D₅-1a** and **1a** and was found to be $K_D/K_H = 4.1$. This interprets that the C-H bond activation step probably is the rate-determining step (Scheme 5B).

Based on the deuterium labeling mechanistic studies and available literature, we depicted the catalytic cycle. The foremost step involves the *ortho* C-H activation of **1a** with the active rhodium catalyst **A**, which yields five-membered rodacycle **B**. Subsequently, the co-ordination of **2a** leads to **C**, which undergoes migratory insertion to generate seven-membered rodacycle **D**. The β -hydride elimination of **D** produces **3a'**, which undergoes enol isomerization to yield the desired product **3a** with concomitant regeneration of the Rh(III) catalyst for the next catalytic cycle (Scheme 6).

In conclusion, we have developed efficient Rh(III)-catalyzed C-H functionalization of *N*-nitrosoanilines using substituted allyl alcohols. The protocol was applied to a wide range of substrates which gave good yields of products with high functional group tolerance. The protocol provides rapid access for one-pot C-H activation and, also, feasible C-H activation of *N*-nitrosoanilines with α,β -unsaturated carbonyls. Low catalyst loading, great functional group tolerance, and superior reactivity of *N*-nitrosoanilines with substituted allyl alcohols are some of the key features of this protocol.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

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Author contributions

PC: conceptualization, formal analysis, investigation, methodology, project administration, resources, validation, writing—original draft, and writing—review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

PC would like to thank Yeungnam University for providing research laboratory and chemical facility for performing the experiments. PC would also like to thank the University of Lucknow for providing basic facilities for manuscript preparation.

Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fchem.2024.1506493/full#supplementary-material>

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